REMARKS

Claims 3-6, 8, 14-16, 24, 36 and 44 were cancelled. Claims7, 9,

Applicants amended Claims 7, 9, 11, 13, 34-35 and 37, limiting those claims to specific compounds disclosed within the specification. Support for this amendment may be found at pages 28-31 of the specification.

Applicants reserve the right to file divisional applications to any subject matter cancelled herein.

35 U.S.C § 112 (1st Par.) Rejection of Claims 3-9, 13-16, 24, 33-38 and 44.

The Examiner rejected Claims 3-9, 13-16, 24, 33-38 and 44 under 35 U.S.C. § 112 (1st Par.), contending that the specification is not enabling for NPY inhibitors (other than B1BP3226) that are selective for an NPY receptor associated with male genitalia.

Applicants traverse the rejection of these claims. In the interest of proceeding forward with prosecution of this case, however, Applciants cancelled Claims 3-6, 8, 14-16, 24, 36 and 44 were cancelled. Applicants amended Claims 7, 9, 11, 13, 34 and 35 such that those claims are now directed to specific NPY inhibitor compounds.

This amendment obviates the 35 U.S.C. § 112 (1st Par.) rejection. Accordingly, Applicants believe that Claims 7, 9, 11, 13, 33-35, 37 and 38 are in a condition for allowance.

35 U.S.C § 103(a) Rejection of Claims 3-9, 13-16, 24, 33 and 44.

The Examiner rejected Claims 3-9, 13-16, 24, 33 and 44 under 35 U.S.C. § 103(a) as unpatentable over Hutchison (WO 98/03492) and Gregor (WO 98/07420). The Examiner contends that Hutchison teaches NPYi ligands and methods of treating disorders, including, but not limited to, sexual dysfunction and reproductive disorders, as well as abnormal drink and food intake such as obesity, anorexia, bulimia and metabolic disorders.

The Examiner contends that Gregor teaches the compound 50 of the instant application and that the compound is useful as a feeding suppressant.. According to the Examiner, Gregor also teaches compositions possessing vasodilating activities, capable of beneficially affecting the reperfusion of ischemic organs.

The Examiner acknowledges that neither reference expressly teaches that neuropeptide inhibitors can increase intracavernosal pressure. The Examiner also admits that the references do not teach the claimed timing of dosing (i.e. before or during sexual arousal).

According to the Examiner, however, one of ordinary skill in the art would be motivated by disclosures of the NPY inhibitors in Hutchison and Gregor for a method of treating MED by increasing intracavernosal pressure, because the NPYi of Hutchison or Gregor are known to be useful to increase blood flow perfusion. Increasing blood perfusion in the male genitalia would cause the increase of intracavernosal pressure and thereby erection.

Applicants traverse the rejection of Claims 7, 9, 13, 33 and 44. In particular, Applicants note that Hutchison *et al.* states that NPY antagonists may be used in those disorders that are associated with inappropriate stimulation of NPY receptors, regardless of the amount of NPY present, and that one of these many disorders is sexual dysfunction.

First, the Applicant is not aware of any data to support the assertion that sexual dysfunction is due to inappropriate stimulation of NPY receptors. Second, as previously argued, sexual dysfunction is a broad term that not only encompasses male erectile dysfunction (MED), but also encompasses many other diseases and disorders that affect sexual function (*e.g.*, female sexual dysfunction (FSD) and premature ejaculation (PE)). Thus, it is respectfully considered that Hutchison *et al.* does not specifically teach the present invention – the treatment of male erectile dysfunction.

The Gregor *et al.* reference states that NPY antagonists are vasodilating agents that can beneficially affect the reperfusion of ischemic organs. Applicants respectfully point out that ischemic reperfusion is distinct from general physiological vasodilatation. Since the penis is not an ischemic organ, there is no reason to suggest that this ischemic dilatation would be applicable to the penile vasculature. Moreover, ischemia is known to be associated with increased NPY levels, and so while one would expect that NPY antagonists would be beneficial to ischemic organs, MED is not known to be associated with increased NPY levels. Accordingly, the Gregor reference does not teach that NPY inhibitors increase blood flow perfusion to the penis.

In light of the above, Applicants submit that the combination of Gregor and Hutchison do not arrive at Applicant's invention – the use of particular NPY inhibitors for

the treatment of MED. Furthemore, the combination of the references do not suggest Applicants' invention either. As admitted by the Examiner, neither reference teaches that NPY inhibitors increase intracavernosal pressure. The Gregor reference teaches increased blood flow perfusion to ichemic organs. There is no teaching or suggestion, however, that such NPY inhibitors increase blood flow to the male genitalia.

There is also no teaching in either reference that such compounds are useful for the treatment of MED. In fact, the art, if anything, teaches away from such use, because of the known association of MED in hypertensive patients. For example, Tong *et al.* (J. Auton. Nerv. Syst., 1996, 56(3): 215-218) clearly shows that NPY immunoreactivity in spontaneously hypertensive rats is increased in genitourinary organs such as the urinary bladder, urethra and prostate, but NOT in the corpus cavernosum. Hypertension is known to be associated with erectile dysfunction, (see, for example, "Hypertension is associated with severe erectile dysfunction", Burchardt et al., 2000 J. Urology, 164, 1188-1191; "The treatment of hypertension in patients with erectile dysfunction", Mikhailidis *et al.*, Curr. Med. Res. Opin., 2000, 16: 31-36; and "Diabetes, hypertension and erectile dysfunction", Ledda, Curr. Med. Res. Opin., 2000, 16: 17-20).

Applicants submit, therefore, that Claims 7, 9, 13, 33 and 44 are not obvious over Hutchinson and Gregor and respectfully request that the Examiner reconsider the rejection thereof.

With respect to the Examiner's response to Applicants' arguments previously presented, the Examiner states that NPY nerve fibers are associated with both penile arteries and veins, but are more abundant in the arteries, thereby implying that an NPY antagonist will be beneficial in MED by preferentially dilating the arteries. Applicants respectfully submit that this conclusion is not valid, especially when taken in conjunction with a publication by Smyth *et al.* (Autonomic Neuroscience: Basic and Clinical, 2000, 86: 18-29). Smyth *et al.* show that NPY nerves are associated with arteries and veins in the guinea pig mesentery, but that NPY (i) does NOT contribute to vasoconstriction of the arteries, and (ii) does contribute to the vasoconstriction of the veins. If one assumes this is the case in the penis then this teaches away from the discovery that NPY antagonists are pro-erectile. With no receptor expression data in penile arteries or veins, it is impossible to state that greater innervation of arteries translates to a greater physiological effect. The NPY nerve fibers to the artery may only act pre-synaptically to limit noradrenaline (NA) release. Inhibition of these would again cause vasoconstriction of the arteries.

A further supporting argument of the contractile effects of NPY being in veins was by published by Kirkeby *et al.* (J. Urology, 1991, 145: 605-609), who investigated the effects of NPY in human penile corpus cavernosum and circumflex veins *in vitro*. The authors clearly demonstrated that NPY only contracted 2 out of 8 corpus cavernosum strips, but was far more successful in contracting circumflex veins (5 out of 8 strips). A separate study by Hedlund and Andersson (Acta Physiol Scand, 1985, 124: 413-419) showed NPY had no effects in corpus cavernosum or cavernous arteries. These data would suggest that a NPY antagonist would not be beneficial in MED and hence would not render the present invention obvious.

The Examiner contends that penile veins are compressed against the tunica albuginea and that it is this mechanism that is responsible for venous occlusion, not vasoconstriction of the veins, is inappropriate. While this mechanism may likely contribute to maintenance of an erection, it will not contribute to initiation of the same. Vasoconstriction of the veins will, however, contribute to penile erections. Indeed, the Wespers *et al.* paper, quoted by the Examiner (Cell Tissue Res., 1988, 254: 69-74), actually states that NPY nerve fibers innervating the penile arteries are likely to contribute to detumesence after ejaculation (page 73, left-hand column, lines 55 to 57), but that the nerve fibers innervating the veins are likely to participate in the reduction of venous outflow and initiation of erections (page 73, right-hand column, lines 24 to 26). Again, here is further evidence that teaches away from the use of NPY antagonists for the treatment of MED.

In further support of Applicants' position that the use of NPY antagonists are not obvious for the treatment of MED, Applicants note the following references:

Hedlund and Andersson (Acta Physiol Scand, 1985, 124: 413-419) investigated the effects of numerous peptides on isolated penile erectile tissue and cavernous artery and found NPY had NO effects. Consequently, this would teach the skilled person away from using an NPY antagonist approach since there are no functional receptors *in vitro* in the erectile tissue.

Before 2001 there were numerous studies in all NPY knockout mice, which included the NPY knockout mouse and NPY1, NPY2, NPY4 and NPY5 receptor knockout mice. As detailed in the review paper by Berglund *et al.* (Experimental Biology and Medicine, 2003, 228(3): 217-244) there were NO effects observed on erectile

function or cardiovascular effects (except the NPY2 knockout mouse, where there was a normal blood pressure response but increased heart rate – Navielhan *et al.*, 1999).

More importantly, NPY over-expressing rats and mice have not had erectile dysfunction reported. In NPY over-expressing mice there have been reports of decreased voluntary ethanol consumption, increased sensitivity to sedative/hypnotic effect of ethanol, and no difference in anxiety-like behaviour (Thiele *et al.*, Nature, 1998, 396: 366-369). In addition, in NPY over-expressing rats, Michalkiewicz *et al.* (Am J Physiol Regul Integr Comp Physiol, 2001, 281: 417-426) have reported normal arterial pressure and heart rate and increased total vascular resistance. Thorsell *et al.* (PNAS, 2000, 97: 12852-12857) have reported reduced stress-related behaviours and impaired spatial memory acquisition. Thus, as there are no reports of erectile dysfunction in these rats and mice, it is therefore argued that it would NOT appear obvious to use NPY antagonists for erectile dysfunction.

Accordingly, Applicants submit that in light of the above, the use of NPY antagonists to treat MED is not an obvious invention.

35 U.S.C. § 103(a) Rejection of Claims 34-38

The Examiner rejected Claims 34-38 as being unpatentable over Hutchison and Viagra monograph June 1999. The Examiner contends that Hutchison teaches NPY1 ligands useful for treating disorders associated with inappropriate stimulation of NPY receptors, including diseases related to sexual dysfunction. The Examiner contends that the Viagra monograph teaches Viagra, a PDE5 inhibitor, useful for treating erectile dysfunction.

The Examiner admits that neither reference expressly teaches both NPY inhibitor and PDE5 inhibitors together for the treatment of MED. The Examiner states, however, that combining two agents known to be useful in treating MED individually into a method useful for the same purpose is prima facie obvious.

Applicants traverse the rejection of Claims 34-38. In particular, Applicants submit that one of ordinary skill in the art would not be motivated to combine the two references to arrive at Applicants invention. Applicants note that Hutchison *et al.* states that NPY antagonists may be used in those disorders that are associated with inappropriate stimulation of NPY receptors, regardless of the amount of NPY present, and that one of these many disorders is sexual dysfunction. As discussed above, Applicant is not aware of any data to support the assertion that sexual dysfunction is due to *inappropriate stimulation* of NPY receptors.

Furthermore, since Hutchison does not teach MED, the combination of NPY and PDE5 inhibitors is not obvious and there is no suggestion in either reference to combine such agents. As previously argued, sexual dysfunction is a broad term that not only encompasses male erectile dysfunction (MED), but also encompasses many other diseases and disorders that affect sexual function (*e.g.*, female sexual dysfunction (FSD) and premature ejaculation (PE)). Thus, it is respectfully considered that Hutchison *et al.* does not teach the present invention – the treatment of male erectile dysfunction. The combination of NPY and PDE5 for the treatment of MED is, therefore, not obvious.

REMARKS

Applicants respectfully request entry of the amendments herein above, and an early examination and allowance of the claims.

Respectfully submitted,

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